UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ANDREW J. DANNENBERG

Appeal No. 2004-1504
Application No. 09/554,604

ON BRIEF

Before, ELLIS, ADAMS and GREEN, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 3-5 and 17. Claims 1, 2, 6, 8 and 12-16 have been canceled. Claims 7 and 9-11 have been withdrawn from consideration by the examiner pursuant to 37 C.F.R. § 1.142.

Claim 3 is illustrative of the subject matter on appeal and reads as follows:

> 3. A method of treating a patient affected with liver disease selected from the group consisting of chronic viral hepatitis B, chronic hepatitis C, alcoholic liver injury and nonalcoholic steatohepatitis, comprising administering to said patient a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2.

The references relied upon by the examiner are:

Gregory et al. (Gregory)	6,172,096	Jan. 9, 2001
Talley et al. (Talley)	5,643,933	Jul. 1, 1997

The references relied upon by the appellant are:

Reuter et al. (Reuter), "Exacerbation of Inflammation-Associated Colonic Injury in Rat through Inhibition of Cyclooxygenase-2," J. Clin. Invest., vol. 98, pp. 2076-2085 (1996).

Mizuno et al., (Mizuno), "Induction of Cyclooxygenase 2 in Gastric Mucosal Lesions and Its Inhibition by the Specific Antagonist Delays Healing in Mice," Gastroenterology, vol. 112, pp. 387-397 (1997).

Mokuno et al. (Mokuno), "Prostaglandin E_1 Protects Against Liver Injury Induced by Escherichia coli Infection via a Dominant Th2-Like Response of Liver T Cells in Mice," Hepatology, vol. 36, pp. 1464-1472 (1999).

Zakim et al. (Zakim), in Hepatology A Textbook of Liver Disease, Volume II, Third Edition, W.B. Saunders Company, Philadelphia (1996), pp. 976 and 977.

Physicians' Desk Reference (PDR) (2001), pp. 2051 and 2484.

Anderson et al. (Anderson), "Failure of Ketoprofen and Interferon Combination Therapy to Improve Interferon-Resistant Chronic Hepatitis C," Can. J. Gastroenterol., vol. 11, pp. 294-297 (1997).

Zarski et al. (Zarski), "Tenoxicam, a Non-Steroid Anti-Inflammatory Drug, Is Unable To Increase the Response Rate in Patients With Chronic Hepatitis C Treated by Alpha Interferon," Hepatology, vol. 27, pp. 862-867 (1998).

Jeng et al. (Jeng), "Secondary Biliary Cirrhosis A Limiting Factor in the Treatment of Hepatolithiasis," Arch Surg, vol. 124, pp. 1301-1305 (1989).

Huizinga, et al. (Huizinga), "Chronic Pancreatitis with Biliary Obstruction," Annals of the Royal College of Surgeons of England, vol. 74, pp. 119-125 (1992).

Claims 3-5 and 17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gregory and Talley.

We have carefully considered the evidence of record which includes the examiner's Answer, the appellant's main Brief and Reply Brief (received November 8, 2002), all the prior art listed above, as well as the declaration of the inventor, Dr. Andrew J. Dannenberg, and find ourselves in agreement with the appellant's position.[1] Accordingly, we reverse.

Background and Discussion

The present invention is said to be directed to a new use for selective inhibitors of cyclooxygenase-2. Specification, p. 1, para. 1. The specification defines the phrase "selective inhibitors of cyclooxygenase-2" as "compound[s] which selectively inhibit[] cyclooxygenase-2 in preference to cyclooxygenase-1 and particularly compound[s] for

[1] In response to an "Order Remanding to Examiner," issued on August 29, 2003, the examiner provided a supplemental Examiner's Answer (mailed December 11, 2003) and the appellant provided a Reply Brief (received December 18, 2003) thereto. However, given our disposition of this case, we need not reach the Yamamoto et al. (Gastroenterology, vol. 125, pp. 556-571 (2003)) publication discussed therein.

which the ratio of the IC_{50} concentration (concentration inhibiting 50% of activity) for cyclooxygenase-1 to the IC_{50} concentration for cyclooxygenase-2 is greater than 1." Id., p. 2, last para. According to the specification, previously "it was considered that cyclooxygenase inhibitors could cause liver injury and for that reason liver disease was not considered as one of the conditions that was treatable by selective inhibitors of cyclooxygenase-2." Id., p. 1, para. 4. The appellant, however, is said to have discovered that the anti-inflammatory properties of said selective inhibitors can be employed for the treatment of select liver diseases. Id., p. 2, paras. 1 and 2.

The examiner argues that Gregory discloses a method of treating a patient having an organ transplant (liver, heart, and kidney), an autoimmune disease or an inflammatory disease such as biliary cirrhosis using a cyclooxygenase-2 inhibitor.[2] Final Office Action, mailed March 21, 2002 in Paper No. 10, p. 3. The examiner further argues that

> . . . it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to employ the compounds herein [taught by Gregory] for treating hepatitis disease because those compounds are known generally to be useful for treating inflammatory diseases and is [sic, are] also known to be useful for treating liver related diseases. Paper No. 10, p. 3.

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[2] We point out that the examiner only relies on Talley for teaching the compounds described in claims 6 and 17. Since (i) claim 6 has been cancelled; and (ii) we find that the examiner has not met his burden of establishing that independent claim 3, from which all the appealed claims depend, would have been obvious to one of ordinary skill in the art, we need not consider the teachings of Talley with respect to the patentability of claim 17.

In response, the appellant argues that selective inhibitors of cyclooxygenase-2 were not known to be generally useful for treating inflammatory disease. Brief, p. 5., para. 1. The appellant relies on Reuter and Mizuno to establish that said selective inhibitors can exacerbate, or delay healing of, inflammation associated with chronic injuries, such as inflammation-associated colonic injury and acute stages of gastric mucosal injury. Id.

The appellant further argues that Gregory does not disclose the treatment of liver diseases generally, but rather, that the patent only mentions liver transplantation rejection and primary biliary cirrhosis (a disease of unknown origin).[3] Brief, p. 6. The appellant points out that Gregory does not provide data on the treatment of the aforementioned liver conditions. Id. The appellant further points out that although Gregory discloses that inhibitors of cyclooxygenase-2 can be used to treat inflammatory bowel disease (IBD), Reuter provides evidence to the contrary. Id. Thus, the appellant contends that, without supporting data, the utilities listed for inhibitors of cyclooxygenase-2 by Gregory are not reliable. Id.

The appellant still further argues that prostaglandins are compounds which are produced by cyclooxygenase-2. Brief, p. 6. According to the appellant, it has long been known that prostaglandins protect "against LPS-induced liver injury by downregulation of the production of inflammatory cytokines." Id., sentence bridging

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[3] In the Reply Brief, the appellant acknowledges that the teachings of Gregory are not limited to the treatment of "primary biliary cirrhosis." Accordingly, we have not considered the appellant's and the examiner's arguments in this regard.

pp. 6-7. Therefore, the appellant contends that the administration of cyclooxygenase-2 inhibitors would "deprive a patient of liver protecting prostaglandin and would be considered as counterindicated in the case of liver diseases." Id., p. 7. The appellant relies on Mokuno (1999) for support.[4]

The appellant still further argues that Zakim (1982)[5] discloses that "hepatotoxicity

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[4] Mokuno discloses that "[t]he incidence of infection with Gram-negative bacteria such as Escherichia coli has increased in recent years among patients undergoing abdominal surgery. These infections frequently result in liver injury and fatal shock, which are caused by endotoxin/LPS derived from Gram-negative bacteria." Mokuno, p. 1464, col. 2, para. 2. Mokuno further discloses that prostaglandins of the E series protect against lipopolysaccharide (LPS)-induced liver damage by down-regulating the production of inflammatory cytokine interleukin 12 (IL-12), and increasing the production of IL-10. Id., the abstract. Mokuno further discloses that prostaglandins "are produced by the action of the enzyme cyclooygenase on arachidonic acid liberated from membrane phospholipids." Id., p. 1464, col. 1, para. 1.

[5] We find that Zakim discloses (p. 976, col. 2), in relevant part, that

> The risk of hepatotoxicity from NSAIDs [non-steroidal anti-inflammatory drugs] has received considerable attention in recent years. The Arthritis Advising Committee of the Food and Drug Administration (FDA) concluded in 1982 that hepatotoxicity is a "class characteristic" of this group of drugs. This unfortunately belies the fact that individual NSAIDs differ widely in their propensity to produce liver damage. Certain agents, including benoxaprofen and ibufenac, produced severe and often fatal hepatotoxicity with such frequency that they were withdrawn soon after introduction. Others, such as meclofenamic acid and fefanamic acid, appear relatively free of hepatotoxic potential. A large retrospective cohort study in Canada estimated the actual increased risk of hepatotoxicity from taking NSAIDs to be quite small, about 5 per 100,000 person-years. Risk factors for the development of liver damage from NSAIDs include advanced age, renal insufficiency, multiple drug use, use of high doses and concomitant alcohol use. Of the currently available NSAIDs in the United States, diclofenac, sulindac, and phenylbutazone appear to carry the greatest risk of hepatotoxicity: piroxicam, ibuprofen, naproxen, and fenoprofen carry an immediate risk. The basis for hepatotoxicity from NSAIDs appears to be largely, but not entirely, idiosyncratic; and cross-sensitivity between different classes of

is class characteristic of NSAIDs [non-steroidal anti-inflammatory drugs] (combination of cyclooxygenase-1/cyclooxygenase-2 inhibitors)." Brief, p. 7.

The appellant still further argues that the PDR discloses that selective inhibitors of cyclooxygenase-2 should not be utilized in patients having liver disorders. Brief, p. 9. The appellant points out that the PDR states that the use of VIOXX is not recommended for patients with moderate to severe hepatic insufficiency and that the use of CELEBREX should be discontinued if liver disease develops. Id. The appellant further argues that VIOXX and CELEBREX are selective inhibitors of cyclooxygenase-2. Id. Thus, the appellant contends that Gregory "has not been accorded the conclusions attributed to it in the office action by those skilled in the art." Id.

The appellant still further argues that all inflammatory liver disorders, including liver transplant and primary biliary cirrhosis[6] and hepatitis are not considered analogous for treatment purposes by those skilled in the art. Brief, p. 10. Thus, the appellant contends that there is no analogy between the liver disorders taught by Gregory and the claimed liver disorders. Id. The appellant relies upon Anderson[7] and

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NSAIDs may occur [footnotes omitted].

[6] See, footnote 3, above.

[7] We find that Anderson discloses (p. 295, col. 1):

> Over the past few years interferon (IFN)-alpha has been widely used to treat chronic infection with hepatitis C virus (HVC). A short term response, however, is seen in only approximately 40% to 50% of treated patients, and the percentage of patients achieving a long term response is significantly less. . . To improve the efficacy of IFN therapy, numerous strategies employing adjuvant therapy have been proposed. . . .

Zarski[8] for support. The appellant contends that Anderson and Zarski "teach away" from the claimed invention and, therefore, the applied prior art does not provide a reasonable expectation of success.

> Certain nonsteroidal anti-inflammatory drugs (NSAIDs), which act as cyclooxygenase inhibitors, reportedly increase the bioavailability of IFN. An in vitro study demonstrated that indomethacin amplifies transduction of the IFN postreceptor signal, leading to an increased biosynthesis of serum 2'5'-oligoadenylate synthetase, an IFN-induced enzyme with antiviral activity. . . .
>
> Recently, small studies have reported that NSAIDs including keoprofen can improve the response to IFN in IFN-resistant chronic hepatitis C patients [footnotes omitted].

Anderson further discloses that, in contrast to the reports by previous investigators, their results show that "there is no benefit in using the combination of ketoprofen with IFN in patients with chronic hepatitis C in whom IFN alone has failed." Anderson, p. 296, col. 2, para. 4; p. 297, col. 1, para. 2. Anderson concludes (p. 297, cols. 1-2) that

> The presence of cirrhosis, which may render a lower response rate to IFN, in nine of the 17 patients may have obscured a possible beneficial effect of ketoprofen. These nine patients, however, were all clinically compensated and probably reflective of many patients with chronic hepatitis C referred for IFN therapy. Our experience is most likely a fair representation of the IFN-unresponsive population for whom adjuvant therapy is desirable [footnotes omitted].

[8] In brief, we find that Zarski discloses (p. 866, col. 1):

> . . . Tenoxicam was not found to increase response rate to IFNα in the treatment of chronic hepatitis C in naive patients. It could be interesting to compare various non-steroid anti-inflammatory drugs because some drugs may have a stronger cyclooxygenase/lipo-oxygenase inhibitory effect. The present study suggests that the inhibitory effect of these drugs if any is probably low.

The appellant still further argues that the examiner has not considered the claimed subject matter as a whole. Reply Brief, p. 2. The appellant contends that said subject matter is directed to treating a patient afflicted with chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury and nonalcoholic steatohepatitis; whereas, Gregory only mentions the treatment of biliary cirrhosis and liver transplant. Id. To that end, the appellant explains that biliary cirrhosis is not the same as alcoholic cirrhosis and the other liver conditions recited in representative claim 3. Reply Brief, p. 3. The appellant further explains that "[c]irrhosis is a general term indicating a progressing liver condition" the progression of which is mediated by the cause; said cause being indicated by the modifier preceding the term cirrhosis. Id. The appellant relies on the teachings of Jeng and Huizinga, for support. According to the appellant, different causes mandate different treatments to stop progression of the cirrhosis. Id. With respect to secondary biliary cirrhosis, the appellant argues that it "is a very uncommon condition that is a consequence of prolonged biliary outflow obstruction." Id., sentence bridging pp. 3-4. The appellant further argues that "[b]iliary cirrhosis, whether primary or secondary, is mediated by obstruction of bile ducts." Id., p. 4. Alcohol cirrhosis, on the other hand, is mediated by alcohol ingestion and does not involve bile duct obstruction. Id.

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72,

223 USPQ 785, 787-88 (Fed. Cir. 1984). It is the examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

In the case before us we find that the originally-filed claims were amended during prosecution. That is, the claims were originally directed to a method of treating any liver disease using a selective inhibitor of cyclooxygenase-2. The claims were subsequently amended to their present form as set forth in claim 3, above. In spite of the amendments, however, the examiner maintained his original position rather than taking a step back and specifically addressing the newly-claimed subject matter and the appellant's arguments and evidence in support thereof. The examiner did not address, in either the final office action or the Answer, the publications provided by the appellant which provide evidence that one having ordinary skill in the art (i) would not employ a selective inhibitor of cyclooxygenase-2 to treat a patient with chronic hepatitis C due to its ineffectiveness (Anderson and Zarski); (ii) understood that a patient being treated with a selective inhibitor of cyclooxygenase-2 was at risk of liver damage (PDR); and (iii) would have understood that given the protective role prostaglandins play in inflammatory disease (Mizuno and Reuter) and that said person would not have been motivated to employ selective inhibitors of cyclooxygenase-2 to treat all the disorders taught by Gregory. Rather, we find that the examiner has only responded to one

publication; viz., the Zakim reference, by stating that the teachings therein don't specifically "lead away from the invention" and, in any event, the Gregory and Talley patents teach that cyclooxygenase-2 inhibitors are generally known for their reduced side effects. Answer, p. 5. We do not find, however, that the sections of the patents relied upon by the examiner are so explicit. Rather, we find that they simply state that the preferred selectivity of the inhibitors for cyclooxygenase-2 may indicate a reduction in the incidence of side effects. No data are provided to support said statement.

In addition, we find that rather than responding to the appellant's arguments, the examiner brushes them aside with sweeping statements such as (i) the "scope of the disorders disclosed in the prior art and the claimed invention are not those presented in appellants [sic, appellant's] arguments;" (ii) Gregory teaches that cyclooxygenase-2 inhibitors are known as being useful "for treating inflammatory diseases generally and biliary cirrhosis specifically, an inflammatory liver disorder, one of ordinary skill in the art would have reasonably expected that cyclooxygenase-2 inhibitor would be useful for treating hepatitis, an inflammatory liver disorder"; and (iii) the "claims including alcoholic liver injury, which would read on alcoholic hepatitis (inflammation) and cirrhosis." Answer, pp. 5-6. Such broadbrush statements do not support a conclusion of obviousness. Obviousness must be based on facts, not unsupported generalities. In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968); In re Freed, 425 F.2d 785, 787, 165 USPQ 570, 571 (CCPA 1970).

In addition to the publication evidence rebutting the examiner's position, we also find the appellant's arguments with respect to the differences between the biliary cirrhosis disclosed in Gregory and the claimed alcoholic liver injury, to be reasonable. Reply brief, pp. 3-4. That is, the appellant argues that (i) secondary biliary cirrhosis is a rare condition that is the "consequence of prolonged biliary outflow obstruction;" (ii) "[b]iliary cirrhosis, whether primary or secondary, is mediated by obstruction of the biled ducts"; whereas, alcoholic cirrhosis is not. Thus, given the differences in the underlying pathology between the liver disorders taught by Gregory and the claimed disorders, we do not find that the teachings of the patent would have suggested the appellant's invention to one of ordinary skill in the art.

Accordingly, in view of the foregoing, we reverse the rejection.

REVERSED

Joan Ellis
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